REMARKS

Claims 17 through 32 are pending.

No fees are considered due at this time, however, if a deficiency occurs, please charge our deposit account number 04-1420 to maintain pendancy.

Rejection of claims 17-32 under 35 U.S.C. § 112, Second paragraph

Claims 17-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention because of the variable of R_1 is further defined into itself, as shown in the group "$C(=O)R_1$".

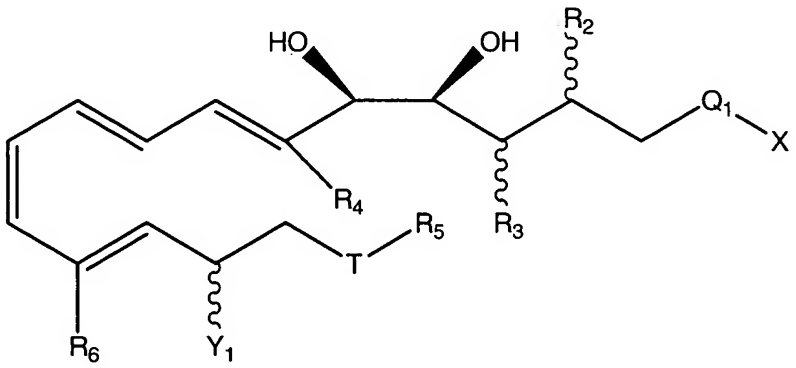
Claims 17, 20, 23, 26, and 29 through 32 have been amended to more clearly define the invention, thereby obviating the basis for this rejection. Reference to the $C(=O)R_1$ group with respect to R_1 has been removed and clarified. Support for this can be found throughout the specification as originally filed.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 17 through 32 under 35 U.S.C. § 103(a)

Claims 17 through 32 are rejected under 35 U.S.C. §103(a) as being unpatentable over "Biochemistry and Cell Biology of Phospholipase D in Human Neutrophils", Chemistry and Physics of Lipids, 80, 3 (1996) (hereinafter "Olson") in view of "Neutrophil-mediated Changes in Vascular Permeability Are Inhibited by Topical Application of Aspirin-triggered 15-epi-lipoxin A_4 and Novel Lipoxin B_4 Stable Analogues" J. Clin. Invest. 101, 819 (1998) (hereinafter "Takano").

The present invention is directed to methods for the modulation of a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation; methods for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation; methods for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity; methods for treatment of PLD initiated superoxide generation or degranulation activity in a subject by the administration of an effective anti-inflammatory amount of a lipoxin analog to the subject. The lipoxin analog has the formula



wherein X is R_1, OR_1, or SR_1;

wherein R_1 is

(i) a hydrogen atom;

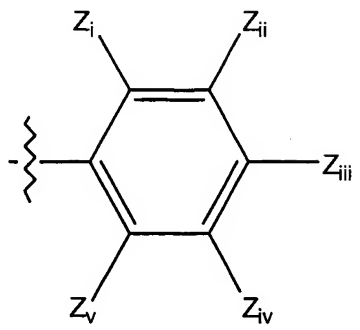
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;

(iii) a cycloalkyl of 3 to 10 carbon atoms;

(iv) an aralkyl of 7 to 12 carbon atoms;

(v) phenyl;

(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-C(=O)-R_T$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or

(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;

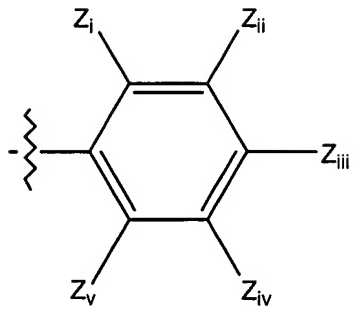
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;

(iii) a cycloalkyl of 3 to 10 carbon atoms;

(iv) an aralkyl of 7 to 12 carbon atoms;

(v) phenyl;

(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

(a) H;

(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;

(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;

(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or

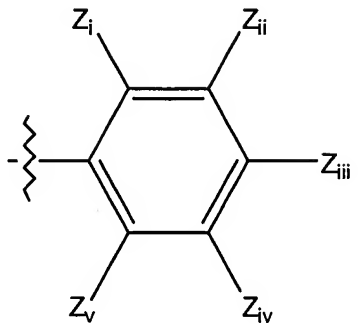
(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;

(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

(a) H;

(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof.

Additionally, the present invention also relates to packaged pharmaceutical compositions which contain the lipoxin analogs and instructions to treat the afflictions described above.

Olson describes a ***biochemical pathway*** for receptor-activated phospholipase -D (PLD) in isolated neutrophils and inflammation.

Olson, the primary reference, fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any therapeutic agent*** to treat a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activity.

Olson, the primary reference, simply describes a biochemical pathway involving PLD. Olson, does not identify, teach or suggest, or provide any motivation or suggestion that treatment of this biochemical pathway would interfere, diminish, or alleviate inflammation in any manner. Olson does not offer a solution to the consequences of PLD involvement in any situation including neutrophil recruitment. Olson, at best, invites a researcher to search for a therapeutic agent that would interfere with the biochemical pathway involving PLD. An invitation to experiment, does not in and of itself, provide a basis for teaching, suggesting, or motivating one skilled in the art that a solution to the problem is at hand. Olson, again at best, provides a problem to be solved.

Applicant has identified the problem (regulation of PLD activity and PMN inflammation) and has addressed the problem, regulation of PLD activity, by interfering with the biochemical pathway with unique and nonobvious compounds, i.e., the lipoxin compounds as presently claimed.

Olson also fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any therapeutic agent*** in ***packaged pharmaceuticals*** with instructions for the treatment of a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activity inflammation in a subject.

Takano, the secondary reference, fails to remedy the deficiencies of Olson. Takano fails to teach or suggest PLD initiated PMN inflammation, let alone a method for modulating or treating a disease or condition associated with PLD initiated PMN inflammation.

Takano fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, as pharmaceuticals capable of modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityin a subject.

Takano also fails to teach or suggest, provide any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, in ***packaged pharmaceuticals*** with instructions for treatment of a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN)

inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityin a subject.

Neither reference, alone or in combination teaches or suggests, provides any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, as pharmaceuticals capable of modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityinflammation in a subject.

Neither reference, alone or in combination, teaches or suggests, provides any motivation or an expectation of success so that one of ordinary skill in the art would utilize ***any of the lipoxin analogs***, described throughout the application, in ***packaged pharmaceuticals*** with instructions for modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation or for treatment of PLD initiated polymorphoneutrophil (PMN) inflammation or for the modulation of a disease or condition associated with PLD initiated superoxide generation or degranulation activity or for treatment of PLD initiated superoxide generation or degranulation activityin a subject.

It is Applicant's position that the Office Action utilizes the combination of references in view of the present invention in a hindsight analysis, which is not permissible by law. In its simplest form, the Office Action makes the argument that any therapeutic method (and hence a therapeutic agent) that might be known to treat inflammation would make it automatically obvious to treat PLD initiated PMN inflammation. The Office Action fails to provide the motivation why the combination

of references would make such a discovery legally obvious. Surely the realization, for example, that a known therapeutic agent could be now used for treatment of PLD initiated PMN inflammation, when it was already known for treatment of inflammation, would result in the non-patentability of that treatment method for any compound. This is not the correct legal standard. No one knew or appreciated that the compound, in the hypothetical example, could be used for such treatment. This analogy mirrors the present case at hand. The discovery and surprise was that the lipoxin compounds of the invention could be used to treat such PLD initiated PMN inflammation. No one had recognized this relationship prior to the presently claimed subject matter; hence the juxtaposition of the impermissible hindsight analysis and/or use of the Applicant's own specification as a blueprint for obviousness.

This becomes an "obvious to try" analysis which is again, not permissible by law. An Applicant's specification and claims cannot be used as a blueprint to solve a previously unknown problem, and then be used against the Applicant.

Therefore, claims 17-32 are in allowable form. Reconsideration and withdrawal of the pending rejection is respectfully requested.

Obviousness-type Double Patenting

Claims 17-32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,353,026.

Upon Notice of Allowance, Applicant is willing to provide a terminal disclaimer with regard to U.S. Patent No. 6,353,026, thereby obviating the basis for this rejection.

Conclusion

In view of the foregoing, Applicant submits that all pending claims distinguish over all references cited by the Examiner and respectfully requests that all rejections be withdrawn. The Examiner is invited to telephone the undersigned attorney for Applicant in the event that such communication is deemed to expedite prosecution of this application.

Attached hereto is a marked up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made."

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: March 27, 2003

By: _____

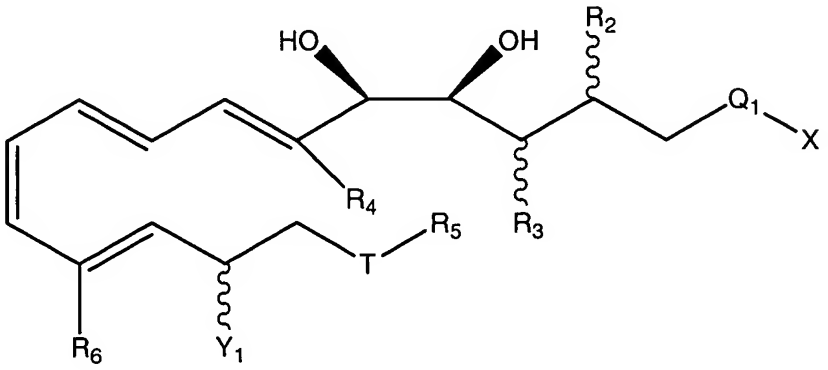
Scott D. Rothenberger
(Reg. No. 41,277)
DORSEY & WHITNEY LLP
Suite 1500
50 South Sixth Street
Minneapolis, MN 55402-1498
Telephone: (612) 340-8819
Facsimile: (612) 340-8856

MARKED-UP VERSION SHOWING CHANGES

In the claims:

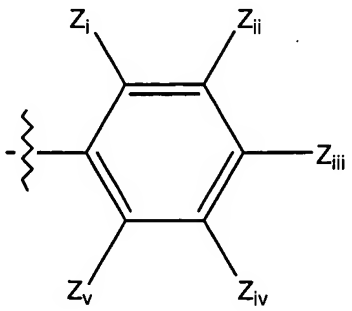
17. (Amended) A method for modulating a disease or condition associated with phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation in a subject, comprising

administering to the subject an effective anti-inflammatory amount of a lipoxin analog having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl

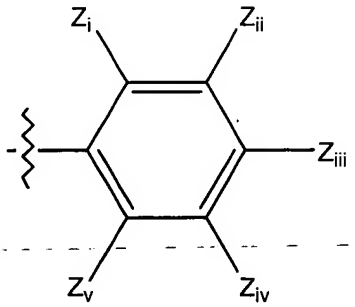


wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $[-C(=O)-R_1]$ $-C(=O)-R_T$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

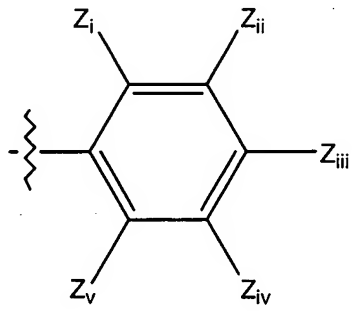
(a) H;

(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or
(e) $R_aQ_2R_b$ wherein Q_2 is -O- or -S-; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

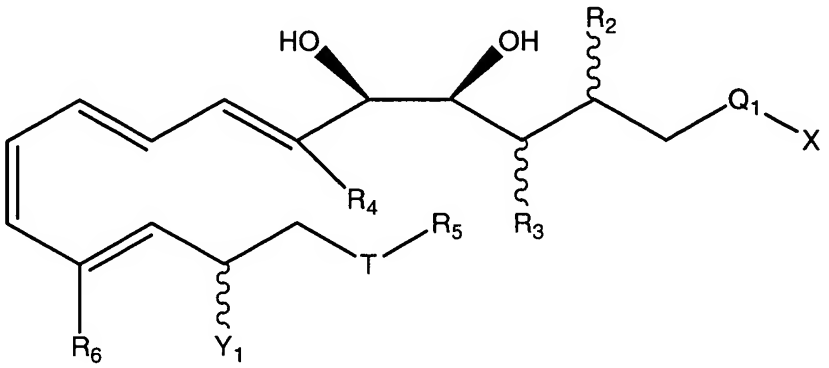
wherein R_6 is

(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof, such that a disease or condition associated with PLD initiated polymorphoneutrophil (PMN) inflammation in a subject is modulated.

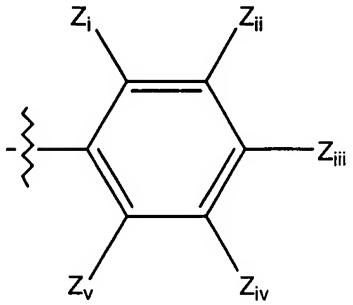
20. (Amended) A method for treating phospholipase D (PLD) initiated polymorphoneutrophil (PMN) inflammation in a subject, comprising

administering to the subject an effective anti-inflammatory amount of a lipoxin analog having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl

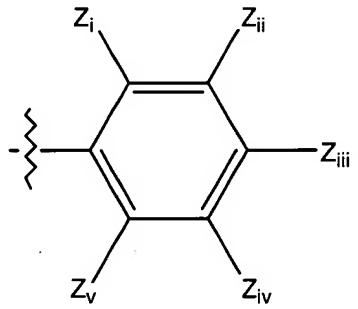


wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, [$-C(=O)-R_1$] $-C(=O)-R_T$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

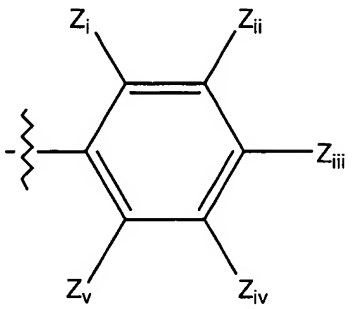
(a) H;
(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or

(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, –CN, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

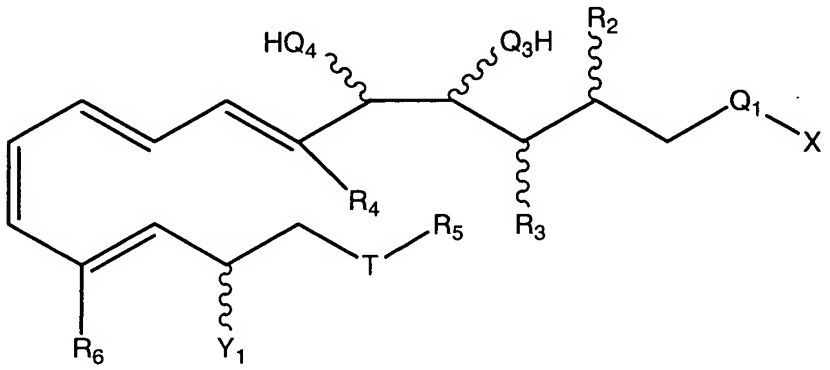
wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

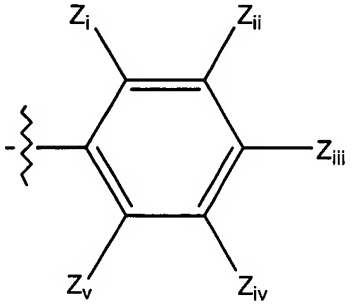
wherein T is O or S, and pharmaceutically acceptable salts thereof, such that PLD initiated polymorphoneutrophil (PMN) inflammation is treated in a subject.

23. (Amended) A method for modulating a disease or condition associated with phospholipase D (PLD) initiated superoxide generation or degranulation activity in a subject, comprising
administering to the subject an effective anti-PLD amount of a lipoxin analog having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl

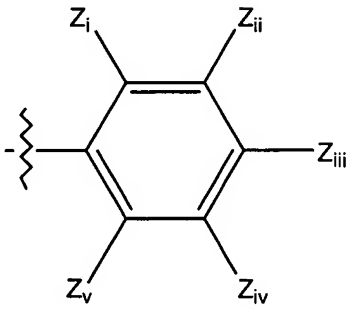


wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, [-C(=O)-R_1] -C(=O)-R_T, $-SO_3H$, a hydrogen atom, halogen, methyl, -OR_x, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

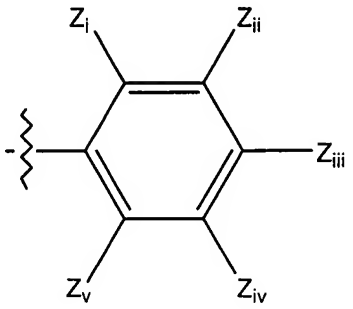
(a) H;
(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or
(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be

straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

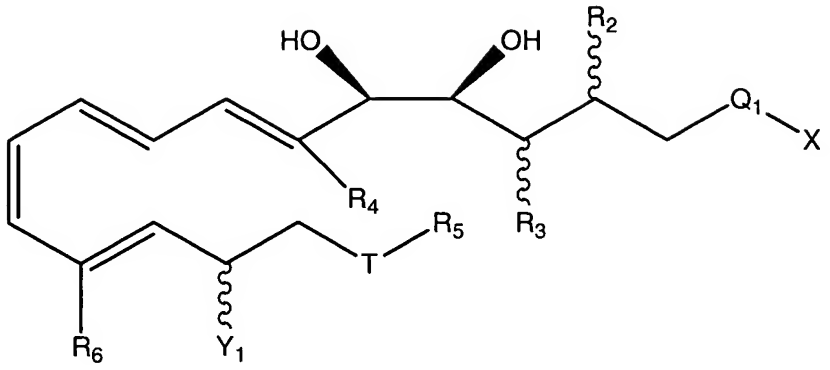
wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

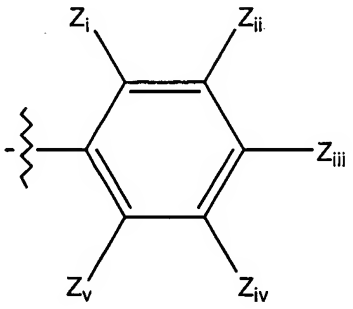
wherein T is O or S, and pharmaceutically acceptable salts thereof, such that a disease or condition associated with PLD initiated superoxide generation or degranulation activity in a subject is modulated.

26. (Amended) A method for treating phospholipase D (PLD) initiated superoxide generation or degranulation in a subject, comprising administering to the subject an effective anti-PLD amount of a lipoxin analog having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl

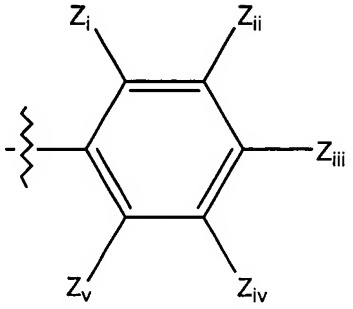


wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $[-C(=O)-R_1]$ $\underline{-C(=O)-R_T}$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

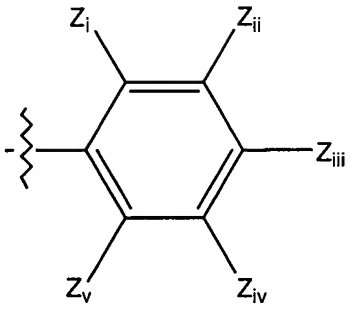
wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

(a) H;
(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or
(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

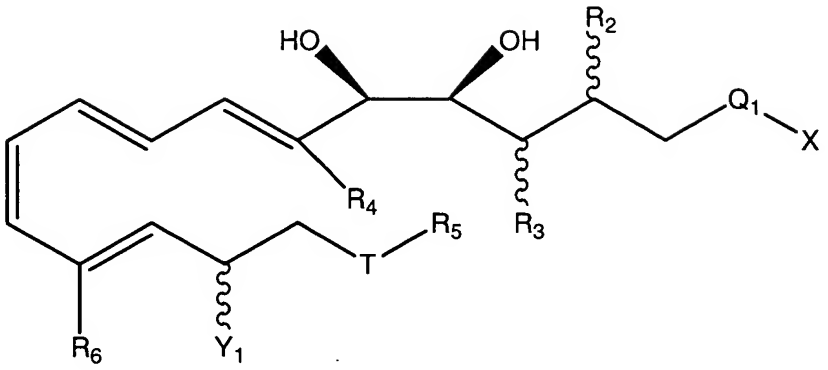
wherein R_6 is

(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof, such that PLD initiated superoxide generation or granulation is treated in a subject.

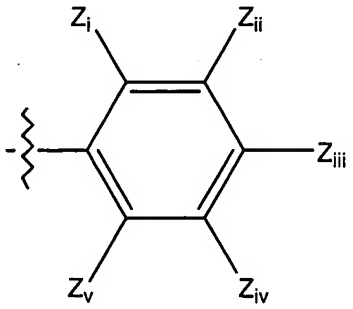
29. (Amended) A packaged pharmaceutical composition for treating a disease or condition associated with phospholipase D (PLD) initiated activity in a subject, comprising:

a container holding a therapeutically effective amount of at least one lipoxin compound having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl

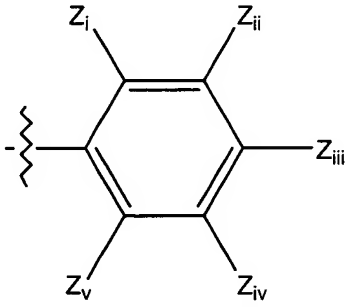


wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, [$-C(=O)-R_1$] $\underline{-C(=O)-R_T}$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

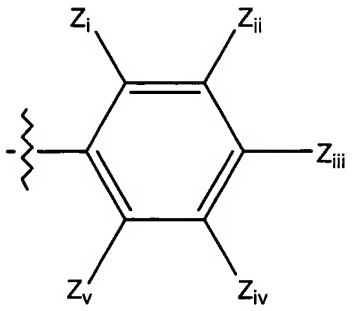
wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

(a) H;
(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or
(e) $R_aQ_2R_b$ wherein Q_2 is –O– or –S–; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

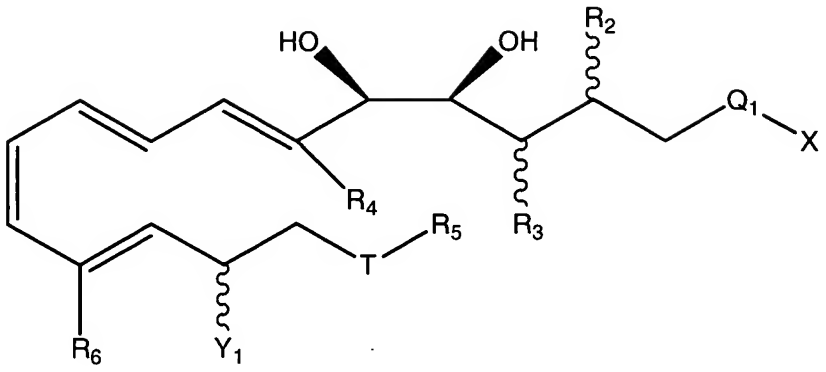
(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof; and

instructions for using said lipoxin compound for treating a disease or condition associated with PLD initiated activity in the subject.

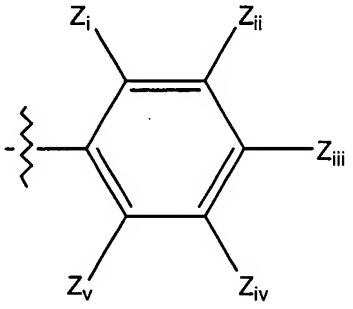
30. (Amended) A packaged pharmaceutical composition for treating phospholipase D initiated activity in a subject, comprising:

a container holding a therapeutically effective amount of at least one lipoxin compound having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



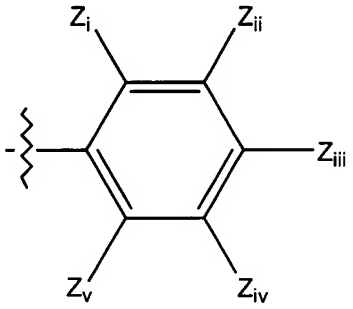
wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, [-C(=O)-R_1] -C(=O)-R_T, $-SO_3H$, a hydrogen atom, halogen, methyl, -OR_x, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or

(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

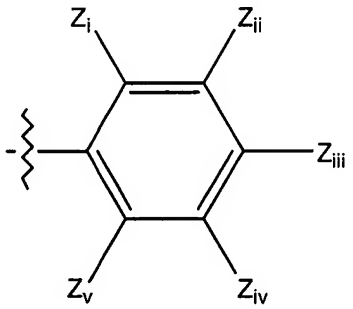
(a) H;
(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or

(e) $R_aQ_2R_b$ wherein Q_2 is -O- or -S-; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

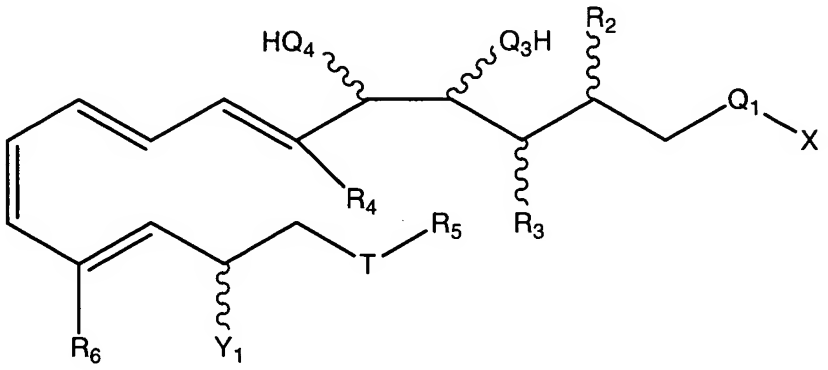
(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof; and

instructions for using said lipoxin compound for treating PLD initiated activity in the subject.

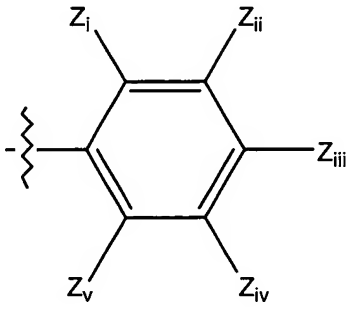
31. (Amended) A packaged pharmaceutical composition for treating a disease or condition associated with phospholipase D (PLD) initiated superoxide generation or degranulation activity in a subject, comprising:

a container holding a therapeutically effective amount of at least one lipoxin compound having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl

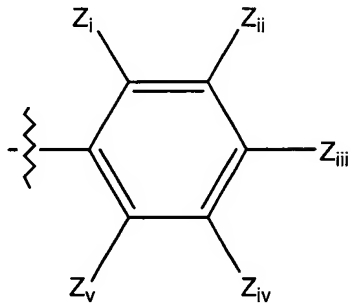


wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, [$-C(=O)-R_1$] $\underline{-C(=O)-R_T}$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

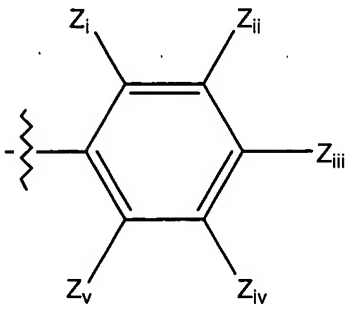
(a) H;
(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or

(e) $R_aQ_2R_b$ wherein Q_2 is -O- or -S-; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

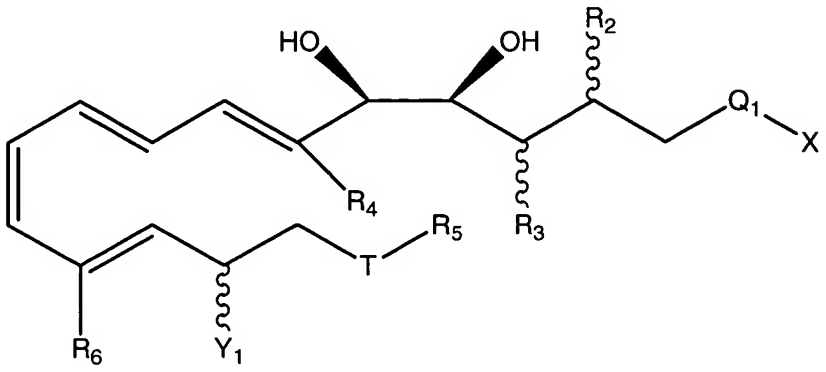
wherein R_6 is

(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof; and
instructions for using said lipoxin compound for treating a disease or condition associated with PLD initiated superoxide generation or degranulation activity in the subject.

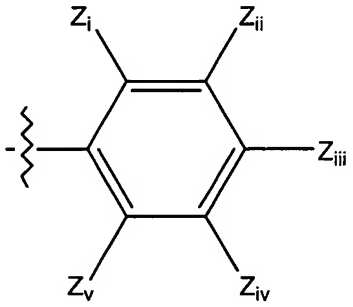
32. (Amended) A packaged pharmaceutical composition for treating phospholipase D (PLD) initiated superoxide generation or degranulation activity in a subject, comprising:

a container holding a therapeutically effective amount of at least one lipoxin compound having the formula



wherein X is R_1, OR_1, or SR_1;
wherein R_1 is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl

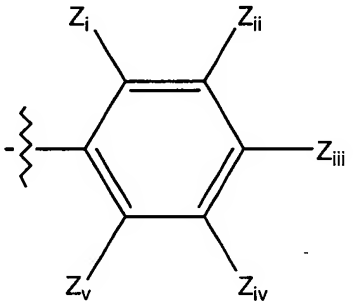


wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $[-C(=O)-R_1]$ $-C(=O)-R_T$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein R_T is

(i) a hydrogen atom;
(ii) an alkyl of 1 to 8 carbons atoms, inclusive, which may be straight chain or branched;
(iii) a cycloalkyl of 3 to 10 carbon atoms;
(iv) an aralkyl of 7 to 12 carbon atoms;
(v) phenyl;
(vi) substituted phenyl



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, $-CN$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl;

(vii) a detectable label molecule; or
(viii) a straight or branched chain alkenyl of 2 to 8 carbon atoms, inclusive;

wherein Q_1 is (C=O), SO_2 or (CN), provided when Q_1 is CN, then X is absent;
wherein Q_3 and Q_4 are each independently O, S or NH;
wherein one of R_2 and R_3 is a hydrogen atom and the other is

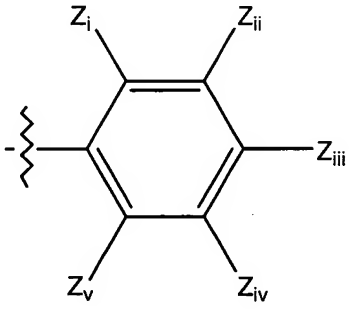
(a) H;

(b) an alkyl of 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched;
(c) a cycloalkyl of 3 to 6 carbon atoms, inclusive;
(d) an alkenyl of 2 to 8 carbon atoms, inclusive, which may be straight chain or branched; or
(e) $R_aQ_2R_b$ wherein Q_2 is -O- or -S-; wherein R_a is alkylene of 0 to 6 carbons atoms, inclusive, which may be straight chain or branched and wherein R_b is alkyl of 0 to 8 carbon atoms, inclusive, which may be straight chain or branched, provided when R_b is 0, then R_b is a hydrogen atom;

wherein R_4 is

(a) H;
(b) an alkyl of 1 to 6 carbon atoms, inclusive, which may be a straight chain or branched;

wherein R_5 is



wherein Z_i, Z_{ii}, Z_{iii}, Z_{iv} and Z_v are each independently selected from $-NO_2$, -CN, $-C(=O)-R_1$, $-SO_3H$, a hydrogen atom, halogen, methyl, $-OR_x$, wherein R_x is 1 to 8 carbon atoms, inclusive, which may be a straight chain or branched, and hydroxyl or a substituted or unsubstituted, branched or unbranched alkyl group;

wherein Y_1 is -OH, methyl, -SH, an alkyl of 2 to 4 carbon atoms, inclusive, straight chain or branched, an alkoxy of 1 to 4 carbon atoms, inclusive, or CH_aZ_b where a+b=3, a=0 to 3, b=0 to 3 and Z is cyano, nitro or a halogen;

wherein R_6 is

(a) H;
(b) an alkyl from 1 to 4 carbon atoms, inclusive, straight chain or branched;

wherein T is O or S, and pharmaceutically acceptable salts thereof; and

instructions for using said lipoxin compound for treating PLD initiated superoxide generation or degranulation activity in the subject.